REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 28-32, 34-37 and 41-43 have been canceled without prejudice, Claims 33, 38-39, 44, 46 and 47 have been amended to clarify what Applicants have always regarded as their invention, and new Claims 48-54 have been added.

Claims 33, 38-40 and 44-54 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. In addition, new Claims 48-54 are fully supported by the specification as originally filed. Support for new Claims 48-54 can be found at least on page 66, lines 31-37, on page 67, lines 3-6, on page 282, lines 12-19 and on page 308, line 38 to page 309, line 7 of the specification.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003 and kindly direct all future correspondence to the address indicated, *i.e.*, to:

CUSTOMER NO. 35489
Ginger R. Dreger
Heller Ehrman White & McAuliffe LLP
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Priority Determination

The Examiner stated that the effective filing date for the application is December 12, 2001, the filing date of the present application.

Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Application Serial No. 60/162,506, filed October 29, 1999, priority to which has been claimed in this application.

As will be shown, the disclosure of the instant application, which is similar to that of the earlier-filed application (U.S. Provisional Application Serial No. 60/162,506, Example 20), provides the support required to establish utility for the claimed polynucleotides. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in U.S. Provisional Application Serial No. 60/162,506. Therefore, the effective filing date of this application is October 29, 1999, the filing date of U.S. Provisional Application Serial No. 60/162,506, and the present application is entitled to at least the October 29, 1999 priority for subject matter defined in Claims 33, 38-40 and 44-54.

Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code, and the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

Double Patenting

The Examiner alleges that "there are a series of applications in which SEQ ID NO:53 is present but do not claim the polynucleotide" and that "there is at least one other application filed by the applicants which contains the polynucleotide of SEQ ID NO:53 which is identical to the

polypeptide of SEQ ID NO:54, and which may contain possible conflicting claims." The Examiner has requested that Applicants point out to the Examiner all double patenting issues.

To the best of our knowledge, Applicants have not filed any applications having claims directed to a polynucleotide of a sequence identical to SEQ ID NO:53. Applicants believe that the Examiner reached his conclusion of the existence of possible conflicting claims based on the disclosure of the **publications** of other U.S. applications filed by Applicants, which do not reflect the changes made in preliminary amendments in those applications.

Deposits of Biological Organisms

Applicants note with appreciation that the Examiner acknowledged the deposit of organisms under accession number ATCC 203287 under the terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure in compliance with this requirement.

Claim Rejections – 35 U.S.C. §101

Claims 28-47 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 5 of the instant Office Action). In particular, the Examiner alleges that "[t]he gene amplification assay is not noted to evidence specific and substantial asserted utility or well established utility because the noted expression is not prescribed to any reasonably likely indication."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 and renders the rejection of these claims moot. Applicants further submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1295 polynucleotide.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed.

Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Utility – Application of Standard

Applicants rely on the gene amplification data for priority and to establish patentable utility for the PRO1295 polynucleotide. Further, the Examiner has admitted that the instant application that the nucleic acid encoding the PRO1780 polypeptide is amplified in primary tumor cell lines including, lung, colon and breast. (See page 6 of the instant Office Action).

However, the Examiner alleges, "Given that PRO1295 sequence was amplified in only a very small number of tumors, and not in tumors of the same type, or all tumors, the data do not support the implicit conclusion that the sequence shows positive correlation sufficient to specifically identify lung, colon or breast cancer."

Applicants respectfully disagree.

Applicants submit that it is well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 7 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

Applicants respectfully submit that the specification discloses that the nucleic acids encoding PRO1295 had ΔCt value of > 1.0, which is **more than 2-fold increase**, in at least 5 of the tumors listed in Table 8. The specification clearly discloses that that significant amplification of nucleic acid DNA59218-1559 encoding PRO1295 occurred (1) in primary lung tumors: HF-000631 and HF-000840; (2) colon tumor centers: HF-000539 and HF-000698; and (3) in breast tumor center HF-000545.

It is also well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1295 is a useful target for therapeutic intervention in lung, colon and breast tumors.

Further, Applicants respectfully submit that the amplification of the nucleic acids in even one lung, colon or breast tumor provides specific and substantial utility for the nucleic acid as a diagnostic marker of the type of lung or colon tumor in which it was amplified. Applicants submit that the tumors listed in Table 8 are not similar tumors from different patients, but various types/classes of lung and/or colon tumors at different stages. Accordingly, a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung/colon/breast tumor, whereas absence of amplification would be non-conclusive.

The Examiner also asserts that "[t]he data presented in the specification were not corrected for aneuploidy." Thus, the Examiner concludes, "A slight amplification of a gene does not *necessarily* mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid."

In response, Applicants respectfully submit a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants respectfully submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker.

Finally, the Examiner alleges, "Even if the data demonstrated a increase in copy number of PRO1295 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent."

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Applicants have amended the claims so the claims only recite the PRO1295 nucleic acids. Hence, the Examiner's rejection regarding the utility of the encoded polypeptide is believe to be moot. Nevertheless, Applicants respectfully submit that Applicants maintain that the utility is provided for the PRO1295 polypeptide.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1295 polypeptide. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101.

Claim Rejection - 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, allegedly since "the claimed invention is not supported by either a specific and substantial utility or a well established utility ...., one skilled in the art clearly would not know how to use the claimed invention" In particular the Examiner notes, "Even if the specification were enabling of how to use the PRO1295 nucleic acids, enablement would not be found commensurate in scope with the claims." (See page 9 of the instant Office Action). The Examiner further asserts that "the specification does not reasonably provide enablement for the variable encoding sequences and for such generic sequences where no requisite functional activity is provided as claimed." (See page 12 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot.

In response to the rejection under 35 U.S.C. §101, Applicants have shown above that the specification discloses a substantial, specific and credible utility for the PRO1295 nucleic acids. In addition, Applicants respectfully submit that as amended, the claims are not drawn to variable encoding sequences for PRO1295. Therefore, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed nucleic acids for the diagnosis of lung, colon and breast tumors; for example, by using diagnostic methods based on hybridization to such amplified sequences.

Further, Applicants respectfully submit that based on the teachings of Example 143 and the general knowledge available in the art at the priority date of the invention, one skilled in the art would be able to practice the claimed invention in its full scope without any undue experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ

428 (Fed. Cir. 1985) M.P.E.P. 2164.01. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-33, 36-37 and 41-47 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 and amendments to Claims 33 and 44 render the rejection of these claims moot.

Accordingly, Applicants respectfully submit that Claims 33, 38-40 and 44-47 satisfy the written description requirement, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Hence, the present rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 28-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In particular, the Examiner objects to the Applicants' use of the terms "extracellular domain" and "lacking its associated signal peptide." The Examiner further asserts that the use of the term "stringent conditions" is indefinite.

Applicants submit that the cancellation of Claims 28-32, 34-37 and 41-43 renders the rejection of these claims moot.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the terms "extracellular domain" and "extracellular domain ... lacking its associated signal peptide" are no longer present in Claim 33 (and, as a consequence, those claims dependent from the same). Hence, the rejection is believed to be moot, and should be withdrawn.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C44**)

Respectfully submitted,

Date: February 7, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

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